April 7, 2009

Roger Citron
State of Montana Medicaid

Dear Mr. Citron:

Your UCB, Inc. Representative Bobby White contacted the Medical Affairs Department with your request for information regarding Keppra® Tablets and Oral Solution (Levetiracetam Immediate-Release). Thank you for letting us know how we can assist you. Specifically, you requested information regarding approval studies.

Keppra®: Approval studies

The package insert for Keppra® (levetiracetam) contains information in the Clinical Studies section. Please review the enclosed package inserts.

Partial Onset Seizures

The effectiveness of Keppra® as adjunctive therapy in the treatment of partial onset seizures in adults was established in three multi-center, randomized, double-blind, placebo-controlled clinical studies. [1,2,3] In these studies, 904 patients both in the United States and Europe, having experienced refractory partial onset seizures for 1-2 years participated. Patients remained on a steady dose of 1-2 antiepileptic drugs (AEDs) and still experienced at least 2 seizures during each 4 weeks of the baseline period. The three well-controlled clinical studies compared either 1000 mg/day, 3000 mg/day Keppra® and placebo, 1000 mg/day, 2000 mg/day Keppra® and placebo or 3000 mg/day Keppra® and placebo given in equally divided, twice daily doses. After the baseline period of 8-12-weeks, patients were randomized to either a Keppra® or placebo treatment group. The 16-18-week treatment period consisted of a 4-6-week titration period, followed by a 12-week fixed dose evaluation period, during which concomitant AED regimens were held constant. The primary measure of effectiveness was a between group comparison of the reduction in weekly partial seizure frequency for the entire treatment period. Secondary measurements included the responder rate (incidence of patients with ≥50% reduction from baseline in partial onset seizure frequency for the entire treatment period).

In all three studies, patients treated with 1000 mg/day, 2000 mg/day or 3000 mg/day Keppra® achieved a statistically significantly greater reduction in weekly partial seizure frequency over placebo. At 1000 mg/day Keppra® patients in Study 1 had a 26.1% and in Study 2 had a 17.1% reduction in partial seizure frequency over placebo. At 2000 mg/day Keppra® patients in Study 2 had a 21.4% reduction in partial seizure frequency over placebo. At 3000 mg/day Keppra® patients in Study 1 had a 30.1% and in Study 3 had a 23.0% reduction in partial seizure frequency over placebo. The responder rate was statistically

significantly greater in patients taking 1000/mg day, 2000 mg/day or 3000 mg/day Keppra® when compared to placebo. At 1000 mg/day Keppra® patients in Study 1 had a 37.1% and in Study 2 had a 20.8% responder rate. At 2000 mg/day Keppra® patients in Study 2 had a 35.2% responder rate. At 3000 mg/day Keppra® patients in Study 1 had a 39.6% and in Study 3 had a 39.4% responder rate. Patients treated with placebo had a 7.4%, 6.3% and 14.4% responder rate for studies 1, 2 and 3 respectively. In these and one other Phase III clinical study, the most frequently reported adverse events when Keppra® was given in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness.

Myoclonic Seizures in Juvenile Myoclonic Epilepsy

Andermann, et al (2005, abstract)[4,5] **evaluated the efficacy and tolerability of Keppra® in 122 patients (age range 12-65 years, including 113 with JME) with idiopathic generalized epilepsy (IGE) experiencing myoclonic seizures in a multicenter, double-blind, placebo-controlled study**. Patients were followed over a 16-week treatment period, consisting of a 4-week titration followed by a 12-week stable-dose evaluation. The primary efficacy endpoint was the responder rate (≥50% reduction in days with myoclonic seizures during the treatment period compared to baseline). Efficacy and safety evaluations were performed in 60 Keppra® and 60 placebo patients. The responder rates for myoclonic seizures were 58.3% for Keppra® and 23.3% for placebo patients, respectively. The median difference in percent reduction between Keppra® and placebo in seizure days per week was 36.55 for myoclonic seizures ($p<0.0001$). Keppra® demonstrated a good tolerability profile.

Primary Generalized Tonic Clinic Seizures

Rosenfeld, et al (2006, abstract) [6,7] **performed a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of adjunctive Keppra® in patients with IGE with primary generalized tonic-clonic (PGTC) seizures**. The intent-to-treat population consisted of 163 patients (age range 4-65 years) with at least three PGTC seizures during an eight-week baseline period, uncontrolled with 1-2 other antiepileptic drugs (AEDs). Patients were randomized to either Keppra® (target dosage 3000 mg/day in adults; 60 mg/kg/day in children) or placebo. The treatment period consisted of a four-week titration period followed by a 20-week stable-dose period. A 28.3% reduction in PGTC weekly seizure frequency was noted in Keppra® patients during the treatment period over placebo ($p=0.004$). A reduction in weekly PGTC seizures of ≥50% was found in 72.2% and 45.2% of Keppra® and placebo patients, respectively ($p=0.0005$). Seizure freedom was achieved in 24.1% and 8.3% of Keppra® and placebo patients, respectively, during the stable-dose period. During the double-blind period, 1.3% of Keppra® patients and 4.8% of placebo patients withdrew due to adverse events.

References:

1. Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I, and the United States Levetiracetam Study Group. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 2000;55(2):236-42.

2. Shorvon SD, Löwenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. Epilepsia 2000;41(9):1179-86.
3. Ben-Menachem E, Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. Epilepsia 2000;41(10):1276-83.
4. Andermann E, Andermann F, Meyvisch P, Vandendriessche A, Schiemann Delgado J. Seizure control with levetiracetam in juvenile myoclonic epilepsies [abstract]. Epilepsia 2005;46(Suppl 8):205.
5. Verdru P, Wajgt A, Schiemann Delgado J, Noachtar S. Efficacy and safety of levetiracetam 3000 mg/d as adjunctive treatment in adolescents and adults suffering from idiopathic generalised epilepsy with myoclonic seizures [abstract]. Epilepsia 2005;46(Suppl 6):56-7.
6. Rosenfeld W, Berkovic SF, Knowlton RC. Efficacy and safety of levetiracetam as adjunctive treatment in adult and paediatric patients suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic seizures [abstract]. Neurology 2006;66(5 Suppl 2):A40.
7. Andermann E, Andermann F, Meyvisch P, Tonner F. Efficacy and tolerability of levetiracetam add-on therapy in patients with refractory idiopathic generalised epilepsy [abstract]. Epilepsia 2006;47(Suppl 4):187.

This material is provided in response to your specific request and may contain information that is not part of the FDA-approved product labeling. If you have additional questions or a patient has experienced an adverse event related to the abovementioned product(s), please contact us toll free at (866) 822-0068, option 9: Medical Information. We appreciate your interest in UCB, Inc., and in our products.

Sincerely,

Joanne Chia
Medical Information Specialist

US-JCH/JCC/4109

Enclosure(s):
Keppra® tablets and oral solution Package Insert